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(54) Title: PROCESS FOR THE PREPARATION OF NAPROXENE NITROXYALKYLESTERS

(57) Abstract: A process for obtaining nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO₂, wherein Y is a C₂-C₂₀ alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as defined containing a cycloalkylene as defined, in the presence of an inorganic base.

PROCESS FOR THE PREPARATION OF NAPROXENE NITROXYALKYLESTERS

* * * * *

The present invention relates to a new method for preparing nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (naproxene) having an enantiomeric excess of the (S) form higher than or equal to 97%, preferably higher than or equal to 98%, combined with high yields, higher than 75-80%, preferably higher than 85%.

It is well known in the prior art that the enantiomeric form (S) is the active form from the pharmacological point of view of the above mentioned product.

In the prior art synthesis methods of nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid, are known. In the patent application WO 98/25,918, a synthesis method of naproxene nitroxyalkyl esters containing in the alkyl chain a saturated C₃-C₈ cycloalkyl residue, is described. In said process the acid or one of its functional derivatives, for example, chloride or anhydride, is reacted, in an inert organic solvent, with a nitroalkanol containing a cycloalkyl residue as above defined. The reaction takes place in the presence of an organic nitrogenated base, such as for example 4-dimethyl aminopyridine, morpholine, N-methyl morpholine or triethylamine. Tests carried out by the Applicant have shown

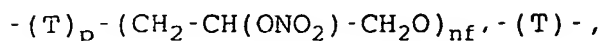
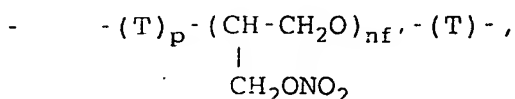
that this process of the prior art does not allow to obtain naproxene nitroxyalkylesters having an enantiomeric excess in the range of 55-80%, only with a specific organic base, 4-N,N-dimethylamino pyridine, 94% is obtained.

The need was therefore felt to obtain naproxene nitroxyalkylesters having an higher enantiomeric excess, at least of 97%, preferably equal to or higher than 98%.

An object of the present invention is a process to obtain nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 97%, preferably higher than or equal to 98%, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acyclic residue of said acid, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO₂, wherein Y has one of the following meanings:

- a linear or optionally branched C₁-C₂₀, preferably C₂-C₅, alkylene;
- a cycloalkylene with ring from 3 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, said cycloalkylene optionally can be substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene;
- an aromatic residue with ring having 5 or 6 carbon atoms,

said aromatic residue optionally can be substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene, or a -COOH group;



T being alkylene as above defined and p an integer equal to zero or one, alkylene having the above mentioned meaning, nf' is an integer from 1 to 6, preferably from 1 to 4; in the presence of an inorganic base, to give the corresponding nitroxyalkylester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-O-Y-ONO₂, wherein A and Y are as above defined.

Y can also be a combination of two or more of the mentioned group.

The aliphatic nitroxyalcohol amount on molar basis is in the range 1-2, preferably 1.2-1.5, with respect to that of the acid halide.

With inorganic bases hydroxides, oxides, carbonates and bicarbonates, silicates, aluminosilicates of the alkaline and alkaline-earth metals, or hydroxides, oxides, carbonates and bicarbonates of metals belonging to the group IIB, preferably zinc, or to groups IIIa or IVa, preferably tin, are meant.

The inorganic base amount is in molar ratio with the acid

halide amount generally in the range 1-2, preferably 1.2-1.5.

With inert organic solvent according to the present invention aromatic hydrocarbons are meant, such as for example toluene and xylene, chlorinated or fluorinated organic solvents, for example methylene chloride, chlorobenzene, aliphatic esters for example C_1 - C_4 acids esters with C_1 - C_5 alcohols such as for example ethyl acetate and butyl acetate, etc.

The solvent amount is not critical and generally from 1 to 10 volumes of solvent are used, preferably from 2 to 5 volumes based on the acid halide weight.

The reaction is carried out at a temperature in the range -20°C and 50°C , preferably 0°C and 20°C .

The nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid are recovered at the end of the reaction, after addition of water to the organic phase, separation of the phases and solvent evaporation. If necessary, a further purification can be carried out by chromatography on silica gel column in order to increase the product titre.

Alternatively, the compound can also be purified by crystallization from a suitable solvent.

Aliphatic nitroxyalcohols can be prepared according to the known methods in the prior art. See for example Gazzetta Chim. It. 1987, 117, 173 and WO 98/25,918.

The Applicant has found that surprisingly by the use of

inorganic bases it is possible to improve the enantiomeric excess of naproxene nitroxyalkylesters with respect to the prior art methods, which use, as seen, organic bases, with high yields as above mentioned.

The following examples have the purpose to illustrate the invention and they are not to be intended as limitative thereof.

EXAMPLE 1 (comparative)

Preparation of 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid according to WO 98/25918

A mixture of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (0.32 g, 1.4 mmol), 4-N,N-dimethylamino pyridine (16 mg, 0.13 mmol), 4-nitroxybutan-1-ol (0.34 g, 2.5 mmol) in dichloromethane (6 ml) at a temperature in the range 0°C-5°C is added, under stirring, to a solution of N,N'-dicyclohexylcarbodiimide (0.29 g, 1.4 mmol) in dichloromethane (6 ml). The mixture is left under stirring at the same temperature for 3 hours and then dried by solvent evaporation under vacuum. The residue is purified by chromatography on silica gel column (eluent dichloromethane) to give the 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (0.41 g, 1.19 mmol), yield 85% in the form of an oil. HPLC purity: 98%.

^1H NMR(CDCl_3) δ (ppm): 1.59 (d, 3H, $J=7.5$ Hz); 1.65 (m, 4H); 3.85 (q, 1H, $J=7.5$ Hz); 3.91 (m, 2H); 4.10 (m, 2H); 7.1-7.7

(m, aromatic, 8H).

Enantiomeric excess: 94%.

EXAMPLE 2

To a solution of 4-nitroxybutan-1-ol (2.0 g; 14.8 mmol) in dichloromethane (20 ml), cooled at 0°C-5°C, potassium carbonate (3.21 g, 23.2 mmol) is added under stirring.

To the mixture a solution of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid chloride (3.86 g, 15.5 mmol; enantiomeric excess 98%) in dichloromethane (22 ml) is added, maintaining the temperature in the range 10°C-15°C. When the addition is over the temperature is increased and maintained for 10 hours at a value in the range 15°C-20°C and then the solution is filtered. The solvent is evaporated under vacuum. The residue is purified by chromatography on silica gel column (eluent dichloromethane) to give the 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (4.4 g, 12.6 mmol, yield 85%) in the form of an oil. HPLC purity: 99%.

¹H NMR(CDCl₃) δ (ppm): 1.59 (d, 3H, J=7.5 Hz); 1.65 (m, 4H); 3.85 (q, 1H, J=7.5 Hz); 3.91 (m, 2H); 4.10 (m, 2H); 7.1-7.7 (m, aromatic, 8H).

Enantiomeric excess: 98%.

EXAMPLE 3

Example 2 is repeated using toluene as solvent. The nitroxyester yield is 76%, the (HPLC) purity > 99%. The enantiomeric excess is equal to 98%.

EXAMPLE 4

Example 2 is repeated but using as a base calcium carbonate. 4.6 g, equal to 13.3 mmols of nitroxyester (yield 90%) are obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 5

Example 2 is repeated but using as a base calcium aluminosilicate. 4.6 g, equal to 13.3 mmols of nitroxyester (yield 90%) are obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 6

To a solution of 4-nitroxybutan-1-ol (2.0 g; 14.8 mmols) in dichloromethane (20 ml), cooled at a temperature in the range 0°C-5°C, potassium carbonate (3.21 g, 23.2 mmols) is added under stirring.

To the mixture a solution of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid chloride (3.86 g, 15.5 mmols, enantiomeric excess 98%) in dichloromethane (22 ml) is added, maintaining the temperature in the range 10°C-15°C. When the addition is over, the temperature is increased to a value in the range 15°C-20°C for 10 hours and then the solution is filtered. Water (1 ml) and N,N-dimethylformamide (2 ml) are added to the solution and left under stirring at room temperature for 3 hours. At the end the organic phase is separated, washed with water and filtered through a potassium carbonate panel. The solvent is evaporated under vacuum and 4.1 g, equivalent to 11.8 mmols of ester (yield 80%) in the form of an oil, are

obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 7 (comparative)

Example 2 is repeated but using as a base triethylamine. The obtained mixture after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 80%.

EXAMPLE 8 (comparative)

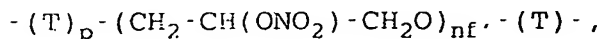
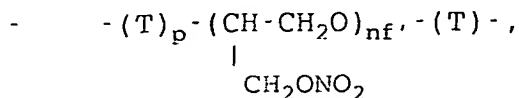
Example 2 is repeated but using as a base diisopropylethylamine. The mixture obtained after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 76%.

EXAMPLE 9 (comparative)

Example 2 is repeated but using as a base N-methylmorpholine. The mixture obtained after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 56%.

CLAIMS

1. A process for obtaining nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 97%, preferably higher than or equal to 98%, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acyl residue of the acid, is let react in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO₂, wherein Y has one of the following meanings:
 - a linear or optionally branched C₁-C₂₀, preferably C₂-C₅, alkylene, or
 - a cycloalkylene with ring from 3 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, said cycloalkylene optionally substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene;
 - an aromatic residue with ring having 5 or 6 carbon atoms, said aromatic residue optionally substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene, or a -COOH group;



T being alkylene as above defined and p an integer equal to zero or one, alkylene having the above mentioned meaning, nf' is an integer from 1 to 6, preferably from 1 to 4;

in the presence of an inorganic base, to give the corresponding nitroxyalkylester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-O-Y-ONO₂, wherein A and Y are as above defined.

2. A process according to claim 1, wherein the aliphatic nitroxyalcohol amount on molar basis is in the range 1-2, preferably 1.2-1.5, with respect to that of the acid halide.
3. A process according to claims 1 and 2, wherein the inorganic bases are hydroxides, oxides, carbonates and bicarbonates, silicates, aluminosilicates of the alkaline and alkaline-earth metals, or hydroxides, oxides, carbonates and bicarbonates of metals belonging to the group IIB, preferably zinc, or to groups IIIa or IVa, preferably tin.
4. A process according to claims 1-3, wherein the inorganic base amount is in molar ratio with the acid halide amount in the range 1-2, preferably 1.2-1.5.

5. A process according to claims 1-4, wherein the reaction is carried out at a temperature in the range -20°C and 50°C , preferably 0°C and 20°C .

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/07222

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 30641 A (NICOX LTD) 16 November 1995 (1995-11-16) examples 1C, 1H ---	1-5
A	WO 97 16405 A (NICOX SA) 9 May 1997 (1997-05-09) example 3 ---	1-5
A	WO 92 01668 A (ITALFARMACO SPA) 6 February 1992 (1992-02-06) page 5, line 19 - line 29; claim 1 ---	1
A	FR 2 757 159 A (HOECHST MARION ROUSSEL INC) 19 June 1998 (1998-06-19) cited in the application claim 7; example 5 --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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PCT/EP 00/07222

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 95 09831 A (NICOX LTD)</p> <p>13 April 1995 (1995-04-13)</p> <p>example 1</p> <p>-----</p>	1

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 00/07222

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9530641 A	16-11-1995	IT 1269735 B	15-04-1997
		IT 1274609 B	18-07-1997
		AT 168986 T	15-08-1998
		AT 184589 T	15-10-1999
		AU 702662 B	25-02-1999
		AU 2215695 A	29-11-1995
		AU 678063 B	15-05-1997
		AU 7809294 A	01-05-1995
		BR 9407749 A	12-02-1997
		BR 9507634 A	23-09-1997
		CA 2173582 A	13-04-1995
		CA 2190087 A	16-11-1995
		DE 69412109 D	03-09-1998
		DE 69412109 T	21-01-1999
		DE 69512232 D	21-10-1999
		DE 69512232 T	24-02-2000
		DK 722434 T	16-11-1998
		DK 759899 T	20-12-1999
		WO 9509831 A	13-04-1995
		EP 0722434 A	24-07-1996
		EP 0759899 A	05-03-1997
		ES 2120070 T	16-10-1998
		ES 2139199 T	01-02-2000
		GR 3032078 T	31-03-2000
		HU 74446 A	30-12-1996
		HU 75961 A	28-05-1997
		JP 9503214 T	31-03-1997
		JP 9512798 T	22-12-1997
		RU 2136653 C	10-09-1999
		SI 722434 T	31-12-1998
		SI 759899 T	31-12-1999
		US 5700947 A	23-12-1997
		US 5861426 A	19-01-1999
		US 5780495 A	14-07-1998
WO 9716405 A	09-05-1997	IT MI952263 A	30-04-1997
		AT 193883 T	15-06-2000
		AU 709338 B	26-08-1999
		AU 7495096 A	22-05-1997
		BR 9611175 A	30-03-1999
		DE 69608916 D	20-07-2000
		EP 0871606 A	21-10-1998
		ES 2148808 T	16-10-2000
		HU 9802986 A	28-04-1999
		JP 11514636 T	14-12-1999
		SI 871606 T	31-08-2000
		US 6040341 A	21-03-2000
WO 9201668 A	06-02-1992	IT 1243367 B	10-06-1994
		AT 118478 T	15-03-1995
		AU 8097491 A	18-02-1992
		CA 2087442 A	27-01-1992
		DE 69107459 D	23-03-1995
		DE 540544 T	23-09-1993
		DK 540544 T	26-06-1995
		EP 0540544 A	12-05-1993
		ES 2056783 T	16-10-1994
		GR 93300079 T	31-08-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/07222

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9201658 A		HU 63374 A	30-08-1993
		HU 213405 B	30-06-1997
		NO 930215 A	22-01-1993
		US 5589490 A	31-12-1996
		US 5366992 A	22-11-1994
FR 2757159 A	19-06-1998	WO 9825918 A	18-06-1998
WO 9509831 A	13-04-1995	GB 2283238 A	03-05-1995
		IT 1269735 B	15-04-1997
		AT 168986 T	15-08-1998
		AU 678063 B	15-05-1997
		AU 7809294 A	01-05-1995
		BR 9407749 A	12-02-1997
		CA 2173582 A	13-04-1995
		DE 69412109 D	03-09-1998
		DE 69412109 T	21-01-1999
		DK 722434 T	16-11-1998
		EP 0722434 A	24-07-1996
		ES 2120070 T	16-10-1998
		HK 1004916 A	11-12-1998
		HU 74446 A	30-12-1996
		JP 9503214 T	31-03-1997
		RU 2136653 C	10-09-1999
		SI 722434 T	31-12-1998
		US 5700947 A	23-12-1997
		US 5780495 A	14-07-1998
		AT 184589 T	15-10-1999
		AU 702662 B	25-02-1999
		AU 2215695 A	29-11-1995
		BR 9507634 A	23-09-1997
		CA 2190087 A	16-11-1995
		DE 69512232 D	21-10-1999
		DE 69512232 T	24-02-2000
		DK 759899 T	20-12-1999
		WO 9530641 A	16-11-1995
		EP 0759899 A	05-03-1997
		ES 2139199 T	01-02-2000
		GR 3032078 T	31-03-2000
		HU 75961 A	28-05-1997
		JP 9512798 T	22-12-1997
		SI 759899 T	31-12-1999
		US 5861426 A	19-01-1999